REMARKS/ARGUMENTS

After entry of the amendment, claims 1, 5-7 and 31-52 remain pending. Claims 6, 7 and 42 have been amended. Claims 7, 31-34 and 51-52 have been withdrawn, and claims 2-4 have been canceled. Applicants reserve the right to pursue such claims in a continuation or divisional application.
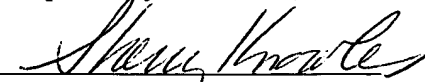
SEQUENCE LISTING

The Examiner has noted that the application does not comply with the requirements of 37 CFR 1.821 through 1.825 for failure to provide sequence identification numbers for all sequences of more than 8 nucleotides or 3 amino acids, particularly regarding page 12 and Seq ID No 19. Applicants enclose herewith a copy of the Notice to Comply with Requirements for Patent Applications containing Nucleotide and/ or Amino Acid Sequence Disclosures, which we believe was filed by the previous Agents for the Applicants (Darby & Darby) on October 28, 2003. This Response included a substitute sequence listing along with the corresponding amendments to the specification to insert the appropriate sequence identifiers. For example, see page 5 of the Response, which amends the specification to insert the appropriate sequence identifiers on page 12; and page 6 of the Response, which inserts Seq ID No 19 in the appropriate text. Applicants believe that the previously submitted Response places the application in compliance with 37 CFR 1.821 through 1.825.

RESTRICTION REQUIREMENT

In response the restriction requirement, Applicants elect Group I, claims 1, 5, 6, 35-50. (Applicants believe that amended claim 42 should now be included as part of the product claim group since it is a further limitation of product claims 41 and 6). Applicants have elected the product claims and reiterate that if the product claims are found allowable, the withdrawn process claims that depend from or otherwise include all of the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04.

It is respectfully believed that this application is ready for examination on the merits. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. The Commissioner is authorized to charge any underpayment of fees and to credit any overpayment to Deposit Account No. 11-0980.
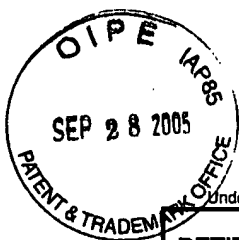
Respectfully submitted,

Sherry M. Knowles, Esq.
Reg. No. 33,052

Date: September 26, 2005

KING & SPALDING LLP
191 Peachtree Street
45th Floor
Atlanta, Georgia 30303-1763
Tel. (404) 572-4600

3857767_1.DOC

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket No. (Optional) 02292/000H795-US0

In re Application of	Lechler and Dorling	
Application Number 09/674,462	Filed	May 8, 2001
For:	IMMUNOSUPPRESSION BY BLOCKING T CELL CO-STIMULATION SIGNAL 2(B7/CD28 INTERACTION)	
Art Unit 1644	Examiner	Jessica Roark

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

[x] One month (37 CFR 1.17(a)(1))	$	110.00
[ ] Two months (37 CFR 1.17(a)(2))	$	
[ ] Three months (37 CFR 1.17(a)(3))	$	
[ ] Four months (37 CFR 1.17(a)(4))	$	
[ ] Five months (37 CFR 1.17(a)(5))	$	

[x] Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $ _____ 55.00 _____ .

[x] A check in the amount of the fee is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[ ] The Director has already been authorized to charge fees in this application to a Deposit Account.

[x] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number _____ 04-0100 _____ .
I have enclosed a duplicate copy of this sheet.

I am the
[ ] applicant/inventor.

[ ] assignee of record of the entire interest. See 37 CFR 3.71.
    Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

[ ] attorney or agent of record. Registration Number _____

[x] attorney or agent under 37 CFR 1.34(a).
    Registration number if acting under 37 CFR 1.34(a) _____ 51,658 _____

| October 28, 2003	_____
Date	Signature
(212) 836-3744	Heather Morehouse Ettinger, Ph.D.
Telephone Number	Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below

[ ] Total of _____ 1 _____ forms are submitted.

Express Mail Label No. _____ Dated: _____
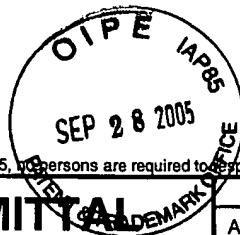
PTO/SB/17 (10-02)
Approved for use through 10/31/2002. OMB 0651-0032
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

FEE TRANSMITTAL
for FY 2003
Patent fees are subject to annual revision.

Complete If Known	
Application Number	09/674,462
Filing Date	May 8, 2001
First Named Inventor	Lechler and Dorling
Examiner Name	Jessica Roark
Group Art Unit	1644
Attorney Docket No.	02292/000H795-US0

[X] Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 55.00

METHOD OF PAYMENT (check all that apply)

[X] Check [ ] Credit Card [ ] Money Order [ ] Other [ ] None

[ ] Deposit Account

Deposit Account Number [ ]

Deposit Account Name [ ]

The Commissioner is hereby authorized to: (check all that apply)

[ ] Charge fee(s) indicated below   [X] Credit any overpayments

[ ] Charge any additional fee(s) during the pendency of this application

[ ] Charge fee(s) indicated below, except for the filing fee

to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Fee ($)	Small Entity Fee Code	Fee ($)	Fee Description	Fee Paid
1001	740	2001	370	Utility filing fee	
1002	330	2002	165	Design filing fee	
1003	510	2003	255	Plant filing fee	
1004	740	2004	370	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims	Fee from below	Fee Paid
Total Claims	[ ] -** = [ ]	x [ ]	= [ ]
Independent Claims	[ ] -** = [ ]	x [ ]	= [ ]
Multiple Dependent		[ ]	= [ ]

Large Entity Fee Code	Fee ($)	Small Entity Fee Code	Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Fee ($)	Small Entity Fee Code	Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for ex parte reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	55.00
1252	400	2252	200	Extension for reply within second month	
1253	920	2253	460	Extension for reply within third month	
1254	1,440	2254	720	Extension for reply within fourth month	
1255	1,960	2255	980	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,280	2453	640	Petition to revive - unintentional	
1501	1,280	2501	640	Utility issue fee (or reissue)	
1502	460	2502	230	Design issue fee	
1503	620	2503	310	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	740	2809	370	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	740	2810	370	For each additional invention to be examined (37CFR 1.129(b))	
1801	740	2801	370	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 55.00

SUBMITTED BY

Name (Print/Type)	Heather Morehouse Ettinger, Ph.D.	Registration No. (Attorney/Agent)	51,658	Telephone	(212) 836-3744
Signature	*Heather Morehouse Ettinger*			Date	October 28, 2003

Complete (if applicable)

Atty Docket No.: 02292/000H795-US0

Inventor: Lechler and Dorling

Appln: 09/674,462   **Filed:** May 8, 2001

Title: IMMUNOSUPPRESSION BY BLOCKING T CELL CO-STIMULATION SIGNAL 2(B7/CD28 INTERACTION)

Documents:

Response to Office Action (11 pages)

One Month Request for Extension of Time Under 37 CFR 1.136(a) (1 page)

Fee Transmittal (1 page)

Transmittal Form (1 page)

Check in the amount of $55.00 *3088*

Tab 1 (2 pages)

Substitute Sequence Listing - paper copy (16 pages)

CRF Substitute Sequence Listing (1 diskette)

Certificate of Express Mailing

Via: Express Mail: Airbill No. *EC 9 8 2 1 0 4 0 9 7 - US*

Sender Initials: HME/   **Date:** October 28, 2003

DBP

DARBY & DARBY P.C.
PATENT OFFICE ACCOUNT
805 THIRD AVENUE
NEW YORK, NY 10022

1-8/210 852   3088

43348074

DATE *10-28-03*

PAY TO THE ORDER OF _____ COMMISSIONER OF PATENTS & TRADEMARKS _____ $ *55 00*

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MEMO *674.462 / 000H795*   *Gabriella V. Karaszi*

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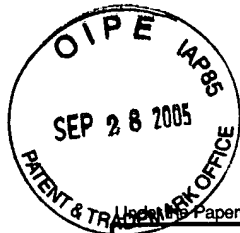
PTO/SB/21 (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/674,462
Filing Date	May 8, 2001
First Named Inventor	Lechler and Dorling
Art Unit	1644
Examiner Name	Jessica Roark

Total Number of Pages in This Submission	1	Attorney Docket Number	02292/000H795-US0

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
  - [x] Fee Attached
- [x] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53

- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____

- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please identify below):

Substitute Sequence Listing (paper and CRF)

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	DARBY & DARBY P.C. Heather Morehouse Ettinger, Ph.D. - 51,658
Signature	*Heather Morehouse Ettinger*
Date	October 28, 2003

Express Mail Label No.	Dated: _____

{W:\02292\000H795-000\00077011.DOC }

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SEP 28 2005
PATENT & TRADEMARK OFFICE
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Customer No.: 07278

File No.: 02292/000H795-US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Lechler and Dorling

Serial No.:   09/674,462   Group Art Unit: 1644

Filed: May 8, 2001   Examiner: Jessica Roark

Confirmation No.:   8594

For: IMMUNOSUPPRESSION BY BLOCKING T CELL CO-STIMULATION SIGNAL 2
       (B7/CD28 INTERACTION)
- -

RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATION CONTAINING NUCLEOTIDE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Notice to Comply with Requirements for Patent Application
containing Nucleotide and/or amino Acid Sequence Disclosures mailed on July 28, 2003, please
consider the following amendments and remarks. Amendments to the specification begin on
page 3 of this paper. Remarks begin on page 9 of this paper. Submitted simultaneously herewith
is (i) a Petition for ONE (1) MONTH Extension of Time up to and including October 28, 2003
accompanied by the required fee, (ii) paper copy of the Substitute Sequence Listing and CRF of

the substitute sequence listing (1 diskette), (iii) fee transmittal sheet, and (iv) Tab 1 (NCBI printout showing sequence disclosed in Parsons et al. reference).

It is believed that no fee other than the fee for one month's extension of time is due. Should the United States Patent and Trademark Office determine that any other fee(s) is due or that any refund is owed for this application, the Commissioner is hereby authorized and requested to charge the required fee(s) and/or credit the refund(s) owed to our Deposit Account No. 04-0100.

AMENDMENTS TO THE SPECIFICATION

On page 4, beginning at line 19, please amend the specification as follows:

In the context of a pig being the donor organism, the invention provides a protein comprising the amino acid sequence shown in Figure 2 as ~~SEQ ID:1~~ SEQ ID NO: 1, which is CTLA-4 cloned from porcine cells. This is the preferred form of CTLA-4 for use in the invention. The extracellular domain of this protein is also shown in Figure 2.

On page 4, beginning at line 23, please amend the specification or follows:

The invention also provides nucleic acid which encodes protein ~~SEQ ID:1~~ SEQ ID NO: 1 (or fragments thereof). This preferably comprises the nucleotide sequence shown in Figure 3 as ~~SEQ ID:2~~ SEQ ID NO: 2.

On page 10, please amend the table as follows:

Domain	Human (SEQ ID NO: 31)	Bovine (SEQ ID NO: 32)
Signal peptide	67.6%	86.5%
Extracellular domain	83.8%	84.6%
Transmembrane domain	96.1%	100%
Cytoplasmic domain	100%	100%
Overall	85.2%	89.2%

On page 11, please amend the table as follows:

Domain	Human (SEQ ID NO: 33)	Bovine (SEQ ID NO: 34)
Signal peptide	76%	81.3%
Extracellular domain	85.2%	86.3%
Transmembrane domain	92.3%	96.2%
Cytoplasmic domain	96.5%	97.7%
Overall	86.1%	88.3%

On page 11, beginning at line 2, please amend the specification as follows:

Figure 4 shows the amino acid sequence of the pCTLA4-Ig construct (SEQ ID NO: 3). The underlined sequence shows the flexible linger GGSGGAA (SEQ ID NO: 28), which also denotes the junction between pCTLA4 and the IgG1 domains.

On page 11, beginning at line 13, please amend the specification as follows:

Figure 8 shows the nucleotide sequence of an anti-human CTLA-4 sFv (SEQ ID NO: 4). The inferred protein sequence is shown in **Figure 9** (SEQ ID NO: 5). **Figure 10** (SEQ ID NOS: 6-9) shows the nucleotide sequences of four anti-murine CTLA-4 sFv. The inferred protein sequences are shown in **Figure 11** (SEQ ID NOS: 10-13). The heavy and light chains are linked by a serine-glycine linker as indicated in Figures 9 and 11.[.]

On page 11, beginning at line 21, please amend the specification as follows:

Figure 15 shows (A) the nucleotide sequence (SEQ ID NO: 14) and (B) the amino acid sequence (SEQ ID NO: 15) of human CTLA-4. The start codon is underlined. At position -21, the sequence differs from GenBank sequence L15006, and at position 110 the sequence differs from both L15006 and M74363.

On page 12, beginning at line 1, please amend the specification as follows:

Figure 16 shows the sequence of cloned human CD8α (SEQ ID NO: 16). This differs from the GenBank sequence at positions 231 (T → G), 244 (A → G), 266 (T → C), and 437 (T → C).

On page 12, beginning at line 17, please amend the specification as follows:

Porcine CTLA-4 ("pCTLA4") was cloned from PHA-activated pig T cells. RNA was prepared using standard techniques and pCTLA4 was amplified by PCR using primers:

5' -TTGAAGCTTAGCCATGGCTTGCTCTGGA- 3' (SEQ ID NO: 17)   (5' primer)

5' -TAATGAATTCTCAATTGATGGGAATAAAATAAG -3' (SEQ ID NO: 18)   (3' primer)

On page 12, beginning at line 25, please amend the specification as follows:

The predicted amino acid sequence of pCTLA4 is shown in figure 2, with a comparison with that of human and cattle. Of significance is the predicted amino acid difference at residue 97, which is important in B7 binding, being part of the conserved hexapeptide motif MYPPPY (SEQ ID NO: 29). In pCTLA4, residue 97 is leucine (giving LYPPPY (SEQ ID NO: 30)), whereas other

species have methionine (although leucine has also been found in bovine CD28 (21)). This important amino acid difference is believed to be of key importance to the advantageous differential binding of pCTLA4 to human and pig B7.

On page 13, line 3, please amend the specification as follows (Please note that the text "**TGCAGCACCACCGGAGCCACC**" has not been added by way of this amendment. This text was underlined in the specification as filed and it should be underlined in the unmarked version of this paragraph.):

The extracellular domain of pCTLA4 was amplified using the 5' primer described above and:

5'-CGGTTC**TGCAG**CACCACCGGAGCCACCATCAGAATCTGGGCATGGTTCTGGAT CAATGAC-3' (SEQ ID NO: 19)

This amplified from position 484, introduced an 18 base-pair segment encoding a linker GGSGGAA (SEQ ID NO: 28) sequence (underlined), and introduced a *Pst*I site (bold) to allow in-frame ligation to the hinge region of human IgG1. The resulting 500bp fragment was sub-cloned into *Hind*III/*Pst*I digested pBluescript-IgG1 containing genomic DNA encoding intronic sequences and the hinge, CH2, CH3 and 3' untranslated exons of human IgG1 between *Pst*I/*Not*I sites. The amino acid sequence of the resulting soluble pCTLA4-Ig is shown in figure 4.

On page 15, beginning at line 7, please amend the specification as follows (Please note that the text "GCGGCCG" and "CTGCAG" has not been added by way of this amendment. This text was underlined in the specification as filed and it should be underlined in the unmarked version of this paragraph.):

The *myc* sequences from pHOOK1 were amplified by PCR using the 5' primer 5'-
GAGCTGAAACGG<u>GCGGCCG</u>CAGAAC-3' <u>(SEQ ID NO: 20)</u>, which contains a *Not*I site
(underlined) and the 3' primer 5'-CTGGC<u>CTGCAG</u>CATTCAGATCC-3' <u>(SEQ ID NO: 21)</u>,
which introduced a *Pst*I site (underlined). The resulting 113 base pair fragment was sub-cloned
into *Not*I/*Pst*I digested pBluescript.

On page 16, beginning at line 7, please amend the specification as follows:

RNA from PHA-activated human T cells was prepared using standard techniques. hCTLA4 was
amplified PCR using primers:

5'-TTCAAAGCTTCAGGATCCTGAAAGGTTTTG-3' <u>(SEQ ID NO: 22)</u> introducing a *Hind*III
site (5' primer)

5'-TAATGAATTCTCAATTGATGGGAATAAAATAAG-3' <u>(SEQ ID NO: 23)</u> introducing a
*Eco*RI site (3' primer)

On page 16, beginning at line 15, please amend the specification as follows
(Please note that the text "<u>ACCACCGGAGCCACC</u>" has not been added by way of this
amendment. This text was underlined in the specification as filed and it should be underlined in
the unmarked version of this paragraph.):

The extracellular domain of hCTLA-4 was amplified using 5' primer described above and:

5'-GATGTAGATATCACAGGCGAAGTCGAC<u>ACCACCGGAGCCACC</u>AATTACATAA
ATCTGGGCTCCGTTGCCTATGCCC-3' <u>(SEQ ID NO: 24)</u>

This amplified from position 457 and included a 15 base segment encoding a flexible GGSGG
<u>(SEQ ID NO: 35)</u> amino acid linker (underlined), along with a unique *Sal*I site (highlighted).

The resulting fragment was sub cloned into *Hind*III/*Eco*RI digested pBluescript and sequenced. hCD8 was PCR-amplified from resting T-cells using primers:

5'-TCGCGCCCAAGCTTCGAGCCAAGCAGCGT-3' (SEQ ID NO: 25) introducing a *Hind*III site (5' primer)

5'-TAATGAATTCTCAATTGATGGGAATAAAATAAG-3' (SEQ ID NO: 26) introducing an *Eco*RI site (3' primer)

On page 16, beginning at line 27, please amend the specification as follows (Please note that the text "GGTGGCTCCGGTGGT" has not been added by way of this amendment. This text was underlined in the specification as filed and it should be underlined in the unmarked version of this paragraph.):

The transmembrane (TM) and cytoplasmic (C) domains of hCD8 were amplified using the 3' primer described above and the following 5' primer:

5'-CATAGGCAACGGAGCCCAGATTTATGTAATTGGTGGCTCCGGTGGTGTCGACT TCGCCTGTGATATCTACATC-3' (SEQ ID NO: 27)

On page 17, beginning at line 1, please amend the specification as follows:

This amplified from position 532 and included a 15 base segment encoding a flexible GGSGG (SEQ ID NO: 35) amino acid linker (underlined), along with a unique *Sal*I site (highlighted). The resulting fragment was sub cloned into *Hind*III/*Sal*I digested pBluescript and called pBluescript-hCD8.

REMARKS

Applicants have carefully studied the Office Action mailed on July 28, 2003, which issued in connection with the above-identified application. The specification has been amended to include the proper identification of all amino acid and nucleotide sequences with sequence identifier numbers (SEQ ID NOS: 1-35). No new matter has been added by way of these amendments.

SUBSTITUTE SEQUENCE LISTING

A Substitute Sequence Listing is being submitted herewith. SEQ ID NO: 34 of the Substitute Sequence Listing is the full-length nucleotide sequence for cattle (bovine) CTLA-4. The cattle CTLA-4 sequence is shown in Figure 3. Nucleotides 296-355 of SEQ ID NO: 34 were accidentally omitted from Figure 3 as filed. A corrected replacement Figure 3 with the full-length cattle CTLA-4 sequence is in preparation and will be submitted in a subsequent submission to the USPTO.

No new matter has been added by way of the Substitute Sequence Listing and, specifically, by way of SEQ ID NO: 34. The specification supports full-length cattle CTLA-4 (SEQ ID NO: 34). In particular, SEQ ID NO: 34 is disclosed in reference 21 cited in the specification (Parsons et al. Immunogenetics 43(6), 388-391 (1996)). A copy of the National

Center for Biotechnology Information printout showing that the Parsons et al. reference

discloses SEQ ID NO: 34 is attached at Tab 1.[1]

STATEMENT PURSUANT TO 37 C.F.R. 1.821(f)

Enclosed herewith is a paper copy and computer readable form (diskette)

containing sequence disclosures. Pursuant to 37 C.F.R. § 1.821(f), Applicants hereby confirm

that the contents of the paper copy of the substitute Sequence Listing filed herewith and entitled

"SEQUENCE LISTING", and of the identically labeled diskette enclosed herewith, specifically

the ASCII-encoded file therein labeled "Seqlist.txt", are identical. This sequence submission

contains no new matter.

Consideration of the enclosed diskette and paper copy of a Substitute Sequence

listing, are respectfully requested.

---

[1]   In addition, SEQ ID NO: 34 was disclosed in and thus, has support in the priority application for the
present application (GB 9809280.2)

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully requested that the application be examined on its merits and that all pending claims be allowed and the case passed to issue.

Respectfully submitted,

Dated: October 28, 2003

Heather Morehouse Ettinger, Ph.D.
Reg. No. 51,658
Agent for Applicants

DARBY & DARBY P.C.
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212-527-7700

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☐ **1:** X93305. B.taurus mRNA for...[gi:1369935]   Links

```
LOCUS       BTCTLA4PT                666 bp    mRNA      linear   MAM 04-JUN-1996
DEFINITION  B.taurus mRNA for CTLA-4 protein.
ACCESSION   X93305
VERSION     X93305.1  GI:1369935
KEYWORDS    CTLA-4 gene; CTLA-4 protein.
SOURCE      Bos taurus (cow)
  ORGANISM  Bos taurus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Cetartiodactyla; Ruminantia; Pecora; Bovoidea;
            Bovidae; Bovinae; Bos.
REFERENCE   1
  AUTHORS   Parsons,K.R., Young,J.R., Collins,B.A. and Howard,C.J.
  TITLE     Cattle CTLA-4, CD28 and chicken CD28 bind CD86: MYPPPY is not
            conserved in cattle CD28
  JOURNAL   Immunogenetics 43 (6), 388-391 (1996)
  MEDLINE   96186531
   PUBMED   8606060
REFERENCE   2  (bases 1 to 666)
  AUTHORS   Parsons,K.R.
  TITLE     Direct Submission
  JOURNAL   Submitted (21-NOV-1995) K.R. Parsons, Institute for Animal Health,
            Division of Immunology and Pathology, Compton, Newbury, Berkshire,
            RG20 7NN, UK
FEATURES             Location/Qualifiers
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     CDS             1..666
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      121 cctccagtgg tgctggctag cagccggggt gttgccagct ctcatgtgatga atatgagtct
      181 tcaggcaaag ctgacgaggt ccgggtgaca gtgctgcggg aggcaggcag ccaggtgacc
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241 gaagtctgtg ctgggacct⬤atggtggag gatgagctaa ccttcctgg⬤gattccact
301 tgcattggca cctccagagg aaacaaagtg aacctcacca tccaagggct gagggccatg
361 gacactgggc tctatgtctg caaagtggag ctcatgtacc cgccgcccta ctacgtgggc
421 atcggcaatg gaacccagat ttacgtcatt gatccagaac catgcccgga ttctgatttt
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541 gctgtttctt tgagcaaaat gctaaagaaa agaagccctc ttactacagg ggtctatgtg
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//

Oct 20 2003 14:38:52

<110> Lechler, Robert
      Dorling, Anthony

<120> IMMUNOSUPPRESSION BY BLOCKING T CELL CO-STIMULATION

<130> 02292/000H795-US0

<140> US 09/674,462
<141> 2001-05-08

<150> PCT/GB99/01350
<151> 1999-04-30

<150> GB-9809280.2
<151> 1998-04-30

<160> 35

<170> PatentIn Ver. 2.1

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<213> Sus scrofa

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Ser Arg Thr Trp Pro Cys Thr Ala Leu Phe Ser Leu Leu Phe Ile Pro
                20   25   30

Val Phe Ser Lys Gly Met His Val Ala Gln Pro Ala Val Val Leu Ala
            35   40   45

Asn Ser Arg Gly Val Ala Ser Phe Val Cys Glu Tyr Gly Ser Ala Gly
        50   55   60

Lys Ala Ala Glu Val Arg Val Thr Val Leu Arg Arg Ala Gly Ser Gln
65   70   75   80

Met Thr Glu Val Cys Ala Ala Thr Tyr Thr Val Glu Asp Glu Leu Thr
                85   90   95

Phe Leu Asp Asp Ser Thr Cys Thr Gly Thr Ser Thr Glu Asn Lys Val
            100   105   110

Asn Leu Thr Ile Gln Gly Leu Arg Ala Val Asp Thr Gly Leu Tyr Ile
        115   120   125

Cys Lys Val Glu Leu Leu Tyr Pro Pro Pro Tyr Tyr Val Gly Met Gly
    130   135   140

Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser
145   150   155   160

Asp Phe Leu Leu Trp Ile Leu Ala Ala Val Ser Ser Gly Leu Phe Phe
            165   170   175

Tyr Ser Phe Leu Ile Thr Ala Val Ser Leu Ser Lys Met Leu Lys Lys
            180   185   190

1

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Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu
        195                 200                 205

Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
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<210> 2
<211> 672
<212> DNA
<213> Sus scrofa

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gcccaacctg cagtagtgct ggccaacagc cggggtgttg ccagctttgt gtgtgagtat 180
gggtctgcag gcaaagctgc cgaggtccgg gtgacagtgc tgcggcgggc cggcagccag 240
atgactgaag tctgtgccgc gacatatact gtggaggatg agttgacctt ccttgatgac 300
tctacatgca ctggcacctc caccgaaaac aaagtgaacc tcaccatcca agggctgaga 360
gccgtggaca ctgggctcta catctgcaag gtggagctcc tgtacccacc accctactat 420
gtgggtatgg caacgggac ccagatttat gtcattgatc cagaaccatg cccagattct 480
gatttcctgc tctggatcct ggcagcagtt agttcagggt tgtttttta cagcttcctc 540
atcacagctg tttctttgag caaaatgcta aagaaaagaa gtcctcttac tacaggggtc 600
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<210> 3
<211> 400
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:pCTLA4-Ig construct (Figure 4)

<400> 3
Met Ala Cys Ser Gly Phe Arg Ser His Gly Ala Trp Leu Glu Leu Thr
  1               5                  10                  15

Ser Arg Thr Trp Pro Cys Thr Ala Leu Phe Ser Leu Leu Phe Ile Pro
                20                  25                  30

Val Phe Ser Lys Gly Met His Val Ala Gln Pro Ala Val Val Leu Ala
            35                  40                  45

Asn Ser Arg Gly Val Ala Ser Phe Val Cys Glu Tyr Gly Ser Ala Gly
        50                  55                  60

Lys Ala Ala Glu Val Arg Val Thr Val Leu Arg Arg Ala Gly Ser Gln
 65                  70                  75                  80

Met Thr Glu Val Cys Ala Ala Thr Tyr Thr Val Glu Asp Glu Leu Thr
                85                  90                  95

Phe Leu Asp Asp Ser Thr Cys Thr Gly Thr Ser Thr Glu Asn Lys Val
            100                 105                 110

Asn Leu Thr Ile Gln Gly Leu Arg Ala Val Asp Thr Gly Leu Tyr Ile
            115                 120                 125

Cys Lys Val Glu Leu Leu Tyr Pro Pro Pro Tyr Tyr Val Gly Met Gly
    130                 135                 140

Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser
                             2
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Asp Gly Gly Ser Gly Gly Ala Ala Glu Pro Lys Ser Cys Asp Lys Thr
            165         170             175

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
            180         185             190

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
        195         200         205

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
    210             215             220

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
225             230             235             240

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
            245             250             255

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
            260             265             270

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
            275             280             285

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
    290             295             300

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
305             310             315             320

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
            325             330             335

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
            340             345             350

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
            355             360             365

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
    370             375             380

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
385             390             395             400
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<210> 4
<211> 722
<212> DNA
<213> Artificial Sequence

<220>
<223> Phage library

<400> 4
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tctcctgtgc agcctctgga ttcacctta gcagctatgc catgagctgg gtccgccagg 120
ctccagggaa ggggctggag tgggtctcag ctattcgtgg tagtggtggt agcacatact 180
acgcagactc cgtgaagggc cggttcacca tctccagaga caattccaag aacacgctgt 240
atctgcaaat gaacagcctg agagccgagg acacggccgt gtattactgt gcaagagctg 300
gtcgtatttt gtttgactat tggggccaag gtaccctggt caccgtctcg agtggtggag 360
gcggttcagg cggaggtggc tctggcggta gtgcacttca gtctgtgctg actcagccac 420
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```
cctcagcgtc tgggacccccc gggcagcggg tcaccatctc ttgttctgga agcagctcca 480
acatcggaag taattatgta tactggtacc agcagctccc aggaacgggc cccaaactcc 540
tcatctatag gaataatcag cggccctcag gggtccctga ccgattctct ggctccaagt 600
ctggcacctc agcctccctg gccatcagtg ggctccggtc cgaggatgag gctgattatt 660
actgtgcagc atgggatgac agcctggtat tcggcggagg gaccaagctc accgtcctag 720
gt                                                                722
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<210> 5
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> Phage library

<400> 5

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
            35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
        50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ala Gly Arg Ile Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            115                 120                 125

Gly Ser Ala Leu Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly
        130                 135                 140

Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn
145                 150                 155                 160

Ile Gly Ser Asn Tyr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala
                165                 170                 175

Pro Lys Leu Leu Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro
            180                 185                 190

Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile
            195                 200                 205

Ser Gly Leu Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp
        210                 215                 220

Asp Asp Ser Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
225                 230                 235                 240
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<210> 6

4

<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Phage library

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ccaggctcca gggaaggggc tggagtgggt ctcagctatt agtggtagtg gtggtagcac 180
atactacgca gactccgtga agggccggtt caccatctcc agagacaatt ccaagaacac 240
gctgtatctg caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcaag 300
agctggtcgt attttgtttg actattgggg ccaaggtacc ctggtcaccg tctcgagtgg 360
tggaggcggt tcaggcggag gtggctctgg cggtagtgca cttcagtctg tgctgactca 420
gccaccctca gcgtctggga cccccgggca gagggtcacc atctcttgtt ctggaagcag 480
ctccaacatc ggaagtaatt atgtatactg gtaccagcag ctcccaggaa cggccccccaa 540
actcctcatc tataggaata atcagcggcc ctcaggggtc cctgaccgat tctctggctc 600
caagtctggc acctcagcct ccctggccat cagtgggctc cggtccgagg atgaggctga 660
ttattactgt gcagcatggg atgacagcct ggtattcggc ggagggacca agctgaccgt 720
cctaggtgc   729

<210> 7
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<223> Phage library

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ccggcagccc ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac 180
caactacaac ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca 240
gttctccctg aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcaag 300
aatgcggaag gataagtttg actattgggg ccaaggtacc ctggtcaccg tctcgagtgg 360
tggaggcggt tcaggcggag gtggctctgg cggtagtgca cttcagtctg tgctgactca 420
gccaccctca gcgtctggga cccccgggca gagggtcacc atctcttgtt ctggaagcag 480
ctccaacatc ggaagtaatt atgtatactg gtaccagcag ctcccaggaa cggccccccaa 540
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caagtctggc acctcagcct ccctggccat cagtgggctc cggtccgagg atgaggctga 660
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cgtcctaggt gcggccgc   738

<210> 8
<211> 739
<212> DNA
<213> Artificial Sequence

<220>
<223> Phage library

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caggcccctg gacaagggct tgagtggatg ggaataatca accctagtgg tggtagcaca 180
caagctacgc acagaagttc cagggcagag tcaccatgac cagggacacg tccacgagca 240
cagtctacat ggagctgagc agcctgagat ctgaggacac ggccgtgtat tactgtgcaa 300
gaatggctcc ctatgtgaat acgcttgttt tttggggcca aggtaccctg gtcaccgtct 360
cgagtggtgg aggcggttca ggcggaggtg gctctggcgg tagtgcactt cagtctgtgc 420
tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc acatgccaag 480
5

taggagacag cctcagaagc tattatgcaa gctggtacca gcagaagcca ggacaggccc 540
ctgtacttgt catctatggt aaaaacaacc ggccctcagg gatcccagac cgattctctg 600
gctccagctc aggaaacaca gcttccttga ccatcactgg ggctcaggcg gaagatgagg 660
ctgactatta ctgtaactcc cgggacagca gtggttttac tgtattcggc ggagggacca 720
agctgaccgt cctaggtgc 739

<210> 9
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Phage library

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tgaagatctc ctgtaagggt tctggataca gctttaccag ctactggatc ggctgggtgc 120
gccagatgcc cgggaaaggc ctggagtgga tggggatcat ctatcctggt gactctgata 180
ccagatacag cccgtccttc caaggccagg tcaccatctc agccgacaag tccatcagca 240
ccgcctacct gcagtggagc agcctgaagg cctcggacac ggccgtgtat tactgtgcaa 300
gattttcgct tggtggtttt gactattggg gccaaggtac cctggtcacc gtctcgagtg 360
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agtctccatg ttcctgtctg catctgtagg agacagagtc accatcactt gccgggccag 480
tcagggcatt agcagttatt tagcctggta tcagcaaaaa ccagggaaag cccctaagct 540
cctggtctat gctgcatcca ctttgcaaag tgggtcccca tcaaggttca gcggcagtgg 600
atctgggaca gaattcactc tcacaatcag cagcctgcag cctgaagatt ttgcaactta 660
ttactgtcaa cagcttaata gttaccgctt gacgttcggc caagggacca agctggaaat 720
caaacgtgc 729

<210> 10
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> Phage library

<400> 10
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Ala Gly Arg Ile Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115   120   125

6

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Gly Ser Ala Leu Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly
    130                 135             140
Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn
145                 150             155                 160
Ile Gly Ser Asn Tyr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala
                165             170                 175
Pro Lys Leu Leu Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro
            180             185                 190
Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile
        195             200                 205
Ser Gly Leu Arg Ser Glu Asp Glu Ala Ser Tyr Tyr Cys Ala Ala Trp
    210             215                 220
Asp Asp Ser Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
225             230                 235                 240
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<210> 11
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Phage library

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Met Ala Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro
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Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Val Ser
            20              25                  30
Ser Gly Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
        35              40                  45
Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn
    50              55                  60
Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn
65              70                  75                  80
Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
            85                  90                  95
Tyr Tyr Cys Ala Arg Met Arg Lys Asp Lys Phe Asp Tyr Trp Gly Gln
            100             105                 110
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115             120                 125
Gly Ser Gly Gly Ser Ala Leu Gln Ser Val Leu Thr Gln Pro Pro Ser
    130             135                 140
Ala Ser Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser
145             150                 155                 160
Ser Ser Asn Ile Gly Ser Asn Tyr Val Tyr Trp Tyr Gln Gln Leu Pro
                165             170                 175
```

7

```
Gly Thr Ala Pro Lys Leu Leu Ile Tyr Arg Asn Asn Gln Arg Pro Ser
            180                 185                 190

Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser
        195                 200                 205

Leu Ala Ile Ser Gly Leu Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Val
    210                 215                 220

Ala Ala Trp Asp Asp Ser Leu Phe Val Phe Gly Gly Gly Thr Lys Leu
225                 230                 235                 240

Thr Val Leu Gly Ala Ala
                245


<210> 12
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Phage library

<400> 12
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Arg Pro Gly Ala
  1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
            35                  40                  45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Val Ala Pro Tyr Val Asn Thr Leu Val Phe Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln Asp Pro Ala Val
    130                 135                 140

Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser
145                 150                 155                 160

Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala
            165                 170                 175

Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro
            180                 185                 190

Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile
        195                 200                 205

Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg
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Asp Ser Ser Gly Phe Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val
225   230   235   240

Leu Gly

<210> 13
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> Phage library

<400> 13
Gln Val Gln Leu Leu Gln Ser Ala Ala Glu Val Lys Lys Pro Gly Glu
 1   5   10   15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
    20   25   30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
    35   40   45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
   50   55   60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65   70   75   80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Val Tyr Tyr Cys
    85   90   95

Ala Arg Phe Ser Leu Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu
    100   105   110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    115   120   125

Gly Ser Ala Leu Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser
  130   135   140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145   150   155   160

Ile Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
    165   170   175

Lys Leu Leu Val Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser
    180   185   190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser
   195   200   205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn
  210   215   220

Ser Tyr Arg Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
225   230   235   240

<210> 14

<211> 742
<212> DNA
<213> Homo sapiens

<400> 14
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aagccatggc ttgccttgga tttcagcggc acaaggctca gctgaacctg gctaccagga 120
cctggccctg cactctcctg ttttttcttc tcttcatccc tgtcttctgc aaagcaatgc 180
acgtggccca gcctgctgtg gtactggcca gcagccgagg catcgccagc tttgtgtgtg 240
agtatgcatc tccaggcaaa gccactgagg tccgggtgac agtgcttcgg caggctgaca 300
gccaggtgac tgaagtctgt gcggcaacct acatgatggg gaatgagttg accttcctag 360
atgattccat ctgcacgggc acctccagtg gaaatcaagt gaacctcact atccaaggac 420
tgagggccat ggacacggga ctctacatct gcaaggtgga gctcatgtac ccaccgccat 480
actacctggg cataggcaac ggaacccaga tttatgtaat tgatccagaa ccgtgcccag 540
attctgactt cctcctctgg atccttgcag cagttagttc ggggttgttt ttttatagct 600
ttctcctcac agctgtttct ttgagcaaaa tgctaaagaa aagaagccct cttacaacag 660
gggtctatgt gaaaatgccc ccaacagagc cagaatgtga aaagcaattt cagccttatt 720
ttattcccat caattgagaa tt 742

<210> 15
<211> 223
<212> PRT
<213> Homo sapiens

<400> 15
Met Ala Cys Leu Gly Phe Gln Arg His Lys Ala Gln Leu Asn Leu Ala
 1   5   10   15

Thr Arg Thr Trp Pro Cys Thr Leu Leu Phe Phe Leu Leu Phe Ile Pro
            20   25   30

Val Phe Cys Lys Ala Met His Val Ala Gln Pro Ala Val Val Leu Ala
        35   40   45

Ser Ser Arg Gly Ile Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly
    50   55   60

Lys Ala Thr Glu Val Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln
65   70   75   80

Val Thr Glu Val Cys Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr
                85   90   95

Phe Leu Asp Asp Ser Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val
            100   105   110

Asn Leu Thr Ile Gln Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile
        115   120   125

Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly
    130   135   140

Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser
145   150   155   160

Asp Phe Leu Leu Trp Ile Leu Ala Ala Val Ser Ser Gly Leu Phe Phe
                165   170   175

Tyr Ser Phe Leu Leu Thr Ala Val Ser Leu Ser Lys Met Leu Lys Lys
            180   185   190

Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu
            195   200   205

10

Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
    210   215   220

<210> 16
<211> 773
<212> DNA
<213> Homo sapiens

<400> 16
aagcttcgag ccaagcagcg tcctggggag cgcgtcatgg ccttaccagt gaccgccttg 60
ctcctgccgc tggccttgct gctccacgcc gccaggccga gccagttccg ggtgtcgccg 120
ctggatcgga cctggaacct gggcgagaca gtggagctga agtgccaggt gctgctgtcc 180
aacccgacgt cgggctgctc gtggctcttc cagccgcgcg cgccgccgc cagtcccacc 240
ttcctcctat acctctccca aaacaagccc aaggcggccg aggggctgga cacccagcgg 300
ttctcgggca agaggttggg ggacaccttc gtcctcaccc tgagcgactt ccgccgagag 360
aacgagggct actatttctg ctcggccctg agcaactcca tcatgtactt cagccacttc 420
gtgccggtct tcctgccagc gaagcccacc acgacgccag cgccgcgacc accaacaccg 480
gcgcccacca tcgcgtcgca gcccctgtcc ctgcgcccag aggcgtgccg gccagcggcg 540
gggggcgcag tgcacacgag ggggctggac ttcgcctgtg atatctacat ctgggcgccc 600
ttggccggga cttgtggggt ccttctcctg tcactggtta tcacccttta ctgcaaccac 660
aggaaccgaa gacgtgtttg caaatgtccc cggcctgtgg tcaaatcggg agacaagccc 720
agcctttcgg cgagatacgt ctaaccctgt gcaacagcca ctacatgaat tcc 773

<210> 17
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 17
ttgaagctta gccatggctt gctctgga 28

<210> 18
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 18
taatgaattc tcaattgatg ggaataaaat aag 33

<210> 19
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 19
cggttctgca gcaccaccgg agccaccatc agaatctggg catggttctg gatcaatgac 60

<210> 20
<211> 25

11

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 20
gagctgaaac gggcggccgc agaac   25

<210> 21
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 21
ctggcctgca gcattcagat cc   22

<210> 22
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 22
ttcaaagctt caggatcctg aaaggttttg   30

<210> 23
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 23
taatgaattc tcaattgatg ggaataaaat aag   33

<210> 24
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 24
gatgtagata tcacaggcga agtcgacacc accggagcca ccaattacat aaatctgggc 60
tccgttgcct atgccc   76

<210> 25
<211> 29
<212> DNA
<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: primer

<400> 25
tcgcgcccaa gcttcgagcc aagcagcgt                                          29


<210> 26
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 26
taatgaattc tcaattgatg ggaataaaat aag                                     33


<210> 27
<211> 73
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 27
cataggcaac ggagcccaga tttatgtaat tggtggctcc ggtggtgtcg acttcgcctg 60
tgatatctac atc                                                          73


<210> 28
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: linker

<400> 28
Gly Gly Ser Gly Gly Ala Ala
  1               5


<210> 29
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: hexapeptide motif

<400> 29
Met Tyr Pro Pro Pro Tyr
  1               5


<210> 30
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
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<223> Description of Artificial Sequence: hexapeptide motif

<400> 30
Leu Tyr Pro Pro Pro Tyr
 1   5

<210> 31
<211> 223
<212> PRT
<213> Homo sapiens

<400> 31
Met Ala Cys Leu Gly Phe Gln Arg His Lys Ala Gln Leu Asn Leu Ala
 1   5   10   15

Ala Arg Thr Trp Pro Cys Thr Leu Leu Phe Phe Leu Leu Phe Ile Pro
            20   25   30

Val Phe Cys Lys Ala Met His Val Ala Gln Pro Ala Val Val Leu Ala
            35   40   45

Ser Ser Arg Gly Ile Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly
        50   55   60

Lys Ala Thr Glu Val Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln
65   70   75   80

Val Thr Glu Val Cys Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr
                85   90   95

Phe Leu Asp Asp Ser Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val
            100   105   110

Asn Leu Thr Ile Gln Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile
        115   120   125

Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly
    130   135   140

Asn Gly Ala Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser
145   150   155   160

Asp Phe Leu Leu Trp Ile Leu Ala Ala Val Ser Ser Gly Leu Phe Phe
            165   170   175

Tyr Ser Phe Leu Leu Thr Ala Val Ser Leu Ser Lys Met Leu Lys Lys
            180   185   190

Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu
        195   200   205

Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
    210   215   220

<210> 32
<211> 221
<212> PRT
<213> Bos taurus

<400> 32
Met Ala Cys Ser Gly Phe Gln Ser His Gly Thr Trp Trp Thr Ser Arg
 1   5   10   15

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```
Thr Trp Pro Cys Thr Ala Leu Phe Phe Leu Val Phe Ile Pro Val Phe
            20              25              30

Ser Lys Gly Met Asn Val Thr Gln Pro Pro Val Val Leu Ala Ser Ser
            35              40              45

Arg Gly Val Ala Ser Phe Ser Cys Glu Tyr Glu Ser Ser Gly Lys Ala
        50              55              60

Asp Glu Val Arg Val Thr Val Leu Arg Glu Ala Gly Ser Gln Val Thr
65              70              75              80

Glu Val Cys Ala Gly Thr Tyr Met Val Glu Asp Glu Leu Thr Phe Leu
            85              90              95

Asp Asp Ser Thr Cys Ile Gly Thr Ser Arg Gly Asn Lys Val Asn Leu
            100             105             110

Thr Ile Gln Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Val Cys Lys
        115             120             125

Val Glu Leu Met Tyr Pro Pro Pro Tyr Tyr Val Gly Ile Gly Asn Gly
    130             135             140

Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Phe
145             150             155             160

Leu Leu Trp Ile Leu Ala Ala Val Ser Ser Gly Leu Phe Phe Tyr Ser
            165             170             175

Phe Leu Ile Thr Ala Val Ser Leu Ser Lys Met Leu Lys Lys Arg Ser
            180             185             190

Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu Pro Glu
        195             200             205

Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
    210             215             220
```

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<210> 33
<211> 672
<212> DNA
<213> Homo sapiens

<400> 33
atggcttgcc ttggatttca gcggcacaag gctcagctga acctggctgc caggacctgg 60
ccctgcactc tcctgttttt tcttctcttc atccctgtct ctgcaaagc aatgcacgtg 120
gcccagcctg ctgtggtact ggccagcagc cgaggcatcg ccagctttgt gtgtgagtat 180
gcatctccag gcaaagccac tgaggtccgg gtgacagtgc ttcggcaggc tgacagccag 240
gtgactgaag tctgtgcggc aacctacatg atggggaatg agttgacctt cctagatgat 300
tccatctgca ccggcacctc cagtggaaat caagtgaacc tcactatcca aggactgagg 360
gccatggaca cgggactcta catctgcaag gtggagctca tgtacccacc gccatactac 420
ctgggcatag caacggagc ccagatttat gtaattgatc cagaaccgtg cccagattct 480
gacttcctcc tctggatcct tgcagcagtt agttcggggt tgtttttta tagctttctc 540
ctcacagctg tttcttttgag caaaatgcta aagaaaagaa gccctcttac aacaggggtc 600
tatgtgaaaa tgcccccaac agagccagaa tgtgaaaagc aatttcagcc ttattttatt 660
cccatcaatt ga 672
```

```
<210> 34
<211> 666
<212> DNA
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15

<210> Bos taurus

<400> 34
atggcttgct ctggattcca gagtcatggg acttggtgga catctaggac ctggccctgc 60
actgccctat tttttcttgt cttcatccct gttttctcta aagggatgaa tgtgacccag 120
cctccagtgg tgctggctag cagccggggt gttgccagct tctcatgtga atatgagtct 180
tcaggcaaag ctgacgaggt ccgggtgaca gtgctgcggg aggcaggcag ccaggtgacc 240
gaagtctgtg ctgggaccta catggtggag gatgagctaa ccttcctgga tgattccact 300
tgcattggca cctccagagg aaacaaagtg aacctcacca tccaagggct gagggccatg 360
gacactgggc tctatgtctg caaagtggag ctcatgtacc cgccgcccta ctacgtgggc 420
atcggcaatg gaacccagat ttacgtcatt gatccagaac catgcccgga ttctgatttt 480
ctcctctgga tcctggcagc agttagttca gggttgtttt tctacagctt cctcatcaca 540
gctgtttctt tgagcaaaat gctaaagaaa agaagccctc ttactacagg ggtctatgtg 600
aaaatgcccc caacagagcc agaatgtgaa aagcaatttc agccttattt tattcccatc 660
aattga 666

<210> 35
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: linker

<400> 35
Gly Gly Ser Gly Gly
 1   5